Complete Summary

GUIDELINE TITLE

Guidelines on the diagnosis and management of AL amyloidosis.

BIBLIOGRAPHIC SOURCE(S)

Guidelines Working Group of UK Myeloma Forum, British Committee for Standards in Haematology, British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol 2004 Jun;125(6):681-700. [62 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

The planned date for full revision of these guidelines by the Guidelines Working Group of the UK Myeloma Forum is January 2007. Interim updates will be on the UK Myeloma Forum and BCSH websites.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Systemic AL amyloidosis (formerly known as primary amyloidosis)

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

The guidelines are intended to set out key areas in the effective diagnosis and clinical management of AL amyloidosis.

TARGET POPULATION

Patients with AL amyloidosis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Pathology
    - Biopsy and histology of screening tissue
    - Congo red staining of marrow biopsy
    - Immunohistochemical staining of tissue biopsy with a panel of antibodies to amyloid fibril proteins
    - Tissue biopsy of affected organ
    - Bone marrow aspirate and biopsy with light chain immunophenotyping
2. Haematology/chemical pathology/immunology
    - Routine electrophoresis and immunofixation of serum and urine
    - Quantifiable serum free light chain (FLC) assay
    - Urea, electrolytes, creatinine, calcium, albumin, 24-hour total protein, liver function test, coagulation screen, creatinine clearance (measured or calculated)
    - Full blood count
    - Quantification of serum and urine paraprotein
    - Levels of normal immunoglobulins
3. Imaging
    - Serum amyloid P component (SAP) scanning
    - Skeletal survey
4. Other
    - DNA analysis
    - Amyloid fibril sequencing
    - Echocardiogram
    - Chest X-ray
    - Organ function assessments

Management/Treatment

1. Chemotherapy and other agents

    - Melphalan with or without prednisolone
    - Vincristine, adriamycin, dexamethasone (VAD)
    - High-dose pulsed dexamethasone (HDD)
    - Intermediate dose melphalan (IDM)
    - Thalidomide
2. High dose therapy and peripheral blood stem cell transplantation
3. General supportive care and organ transplantation
    - Dialysis
    - Renal transplantation
    - Congestive cardiac failure therapy and cardiac transplantation
    - Orthostatic hypotension therapy (fludrocortisone, midodrine)
    - Management of bleeding problems (factor replacement, platelet transfusion, anti-fibrinolytic agents)
4. Experimental approaches to treatment in clinical trials
5. Treatment of multiple myeloma and AL amyloidosis
6. Patient information and support

MAJOR OUTCOMES CONSIDERED

- Response to therapy
- Adverse events
- Quality of life
- Survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

A Medline search for literature published between January 1975 and January 2003 was performed using PubMed. A search was made for clinical trials involving AL (primary) amyloidosis and papers or reviews where AL amyloidosis was the major focus. Abstracts from relevant meetings held between 1998 and 2003 were also included. The Cochrane database was searched but did not include any relevant information.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials

Ib Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case-control studies

IIb Evidence obtained from at least one other type of well-designed, quasi-experimental study (i.e. studies without planned intervention, including observational studies)

III Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Recommendations were made based on literature review and consensus of expert opinion in consultation with representatives of other specialities and patient advocate groups.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendations

Grade A, evidence level Ia, Ib

Recommendation based on at least one randomised controlled trial of good quality and consistency addressing specific recommendation

Grade B, evidence level IIa, IIb, III

Recommendation based on well-conducted studies but no randomised controlled trials on the topic of recommendation

Grade C, evidence level IV

Evidence from expert committee reports and/or clinical experiences of respected authorities

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft guidelines were reviewed by the UK Myeloma Forum Executive, members of the British Committee for Standards in Haematology and a panel of approximately 60 UK haematologists. The British Society of Blood and Marrow Transplantation also reviewed the document.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence **(I–IV)** and strength of recommendations **(A–C)** are defined at the end of the "Major Recommendations" field.

Diagnosis and Investigation

- Maintain a high index of suspicion (**grade B recommendation, level III evidence**)
- Confirm the presence of amyloid on a tissue biopsy (**grade B recommendation, level III evidence**)
- Look for evidence of plasma cell dyscrasias including immunofixation and serum free light chain (FLC) measurements (**grade B recommendation, level III evidence**)
- Consider discussion with/referral to National Amyloidosis Centre (NAC) for exclusion of other forms of amyloidosis (**grade B recommendation, level III evidence**)
- Perform comprehensive assessment of the extent of organ involvement by non-invasive criteria including serum amyloid P component (SAP) scanning when this is feasible (**grade B recommendation, level III evidence**)

Investigations required in suspected AL amyloidosis

	Confirmation of amyloid	Determination of amyloid type	Evaluation of organ involvement	Investigation of underlying plasm cell dyscrasia
Pathology	Biopsy and histology of screening tissue (e.g. fat aspirate or rectal biopsy or affected organ). Congo red staining of marrow biopsy	Immunohistochemical staining of tissue biopsy with a panel of antibodies to amyloid fibril proteins	Tissue biopsy of affected organ, but once the diagnosis is known, organ biopsies merely to determine extent of amyloid involvement not recommended	Bone marrow aspirate and bio with light chain immunophenoty
Haematology/chemical pathology/immunology		Routine electrophoresis and immunofixation of serum and urine. Quantifiable serum FLC assay	Urea, electrolytes, creatinine, albumin 24-h total protein, liver function test, coagulation screen, creatinine clearance (measured or calculated)	FBC, urea and electrolytes, creatinine, calciu albumin. Quantification of serum and urine paraprotein. Lev of normal immunoglobulins
Imaging	SAP scanning	SAP scanning (evidence of marrow involvement)	SAP scanning	Skeletal survey
Other		DNA analysis, amyloid fibril sequencing	ECG; echocardiogram chest X-ray	

Chemotherapy and Other Agents

Colchicine

- There is no role for colchicines in the management of AL amyloidosis (**grade A recommendation, level Ib evidence**)

Melphalan and Prednisolone

- Melphalan with or without prednisolone may be considered as initial treatment of choice for patients in whom intermediate or high-dose therapy (HDT) is not considered appropriate (**grade A recommendation; level Ib evidence**).
- Treatment should be continued when feasible until the clonal disease has been substantially suppressed (i.e. by at least 50–75%, or until plateau) and should be monitored where possible by the serum FLC assay (**grade C recommendation; level IV evidence**)
- The evidence of benefit from steroids in standard doses has not been evaluated in AL amyloidosis. In myeloma the evidence of benefit from steroids in standard doses is controversial. It may therefore be reasonable not to include prednisolone, particularly in patients at risk of steroid-related side effect (**grade C recommendation; level IV evidence**).

Combination Chemotherapy

- There is no role for the use of VBMCP (vincristine, carmustine, melphalan, cyclophosphamide, prednisone) in the management of AL amyloidosis (**grade A recommendation; level Ib evidence**).
- There is no evidence to support the use of other alkylator-based combination regimens such as ABCM (adriamycin, bleomycin, cyclophosphamide, mitomycin-C) or VMCP (vincristine, melphalan, cyclophosphamide, prednisone)-VBAP (vincristine, carmustine, adriamycin, prednisone).

Interferon (IFN)-alpha2b

- There is no role for the use of IFN-alpha2b in the management of AL amyloidosis (**grade B recommendation; level IIa evidence**).

Vincristine, Adriamycin, Dexamethasone (VAD)

- VAD should be considered as first-line therapy in patients under the age of 70 years who do not have symptomatic cardiac failure, autonomic neuropathy or peripheral neuropathy (**grade B recommendation; level III evidence**).
- Careful monitoring is required because of increased risk of toxicity in these patients (**grade C recommendation; level IV evidence**).

High-Dose Pulsed Dexamethasone (HDD)

- HDD may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those who are refractory to chemotherapy (**grade B recommendation; level IIa evidence**).

Intermediate-Dose Melphalan (IDM)

- Intermediate dose melphalan may be considered in patients who are fit for intravenous therapy, but in whom VAD is contraindicated or has produced an inadequate response (**grade C recommendation; level III evidence**).
- Stem cell harvesting prior to treatment with IDM should be considered in patients who might subsequently benefit from peripheral blood stem cell transplantation (PBSCT) as the IDM regimen may deplete stem cell reserves (**grade C recommendation; level IV evidence**).

Thalidomide

- Thalidomide may be considered in patients in whom other regimens may not be feasible due to expected toxicity or in those who are refractory to chemotherapy (**grade C recommendation; level IV evidence**).
- Where possible, patients should be treated in the context of clinical trials (**grade C recommendation; level IV evidence**).

HDT and Autologous Stem Cell Transplantation

- High-dose therapy and PBSCT is not recommended in patients with any of the following:
    - Symptomatic cardiac amyloid
    - Symptomatic autonomic neuropathy
    - History of gastrointestinal bleeding due to amyloid
    - Dialysis-dependent renal failure
    - Age over 70 years
    - More then two organ systems involved
- Peripheral blood stem cell transplantation may be considered in other selected patients, including:
    - Good-risk patients (no cardiac involvement, one to two organs involved and glomerular filtration rate >50 ml/min)
    - Patients treated with VAD or other initial therapy who have not responded
    - Patients with early relapse of plasma cell dyscrasia after VAD or other treatment
- Transplantation should be performed according to an agreed protocol in centres with particular expertise/ interest caution is required during mobilization and harvesting of stem cells prior to transplantation and this should also be performed according to an agreed protocol in centres with particular expertise/interest.

Overview of Treatment

- Present recommendations for choice of therapy are as follows:
    - Where possible, patients should be treated in the context of clinical trials.
    - Patients who are fit enough should receive VAD as initial therapy.
    - IDM should be considered in patients who are fit for intravenous therapy, but in whom VAD is contraindicated or has produced an inadequate response. PBSC harvest should be considered before proceeding with IDM.
    - If not fit for VAD or IDM, the treatment options are as follows, but the evidence base is very small and there have been no comparative, randomized, controlled trials. No firm recommendation can therefore be made, and treatment choice will depend on individual factors.
        - Melphalan and prednisolone (MP): well-tolerated but slow response
        - HDD: rapid response but no data on durability
        - Thalidomide: more data needed
        - Novel therapies
        - Palliative care

- High-dose therapy and PBSCT may be considered in selected patients (see above).
- Supportive care is important in all patients.

General Supportive Care and Organ Transplantation

Renal Failure and Renal Transplantation

- Patients with end-stage renal failure should be considered for dialysis (**grade C recommendation; level IV evidence**).
- Renal transplantation may be considered in selected patients on a case-by-case basis (**grade C recommendation; level IV evidence**).

Congestive Cardiac Failure and Cardiac Transplantation

- Congestive cardiac failure should be treated predominantly with diuretics, and angiotensin-converting enzyme inhibitors should be used with caution (**grade C recommendation; level IV evidence**).
- Calcium-channel blockers and beta-blockers are best avoided in cardiac amyloidosis (**grade C recommendation; level IV evidence**).
- Cardiac amyloidosis is a relative contraindication to the use of digoxin (**grade C recommendation; level IV evidence**).
- In patients where cardiac manifestations are the predominant or only signs/symptoms of cardiac amyloidosis, patients should be considered for heart transplantation but this procedure should be followed by chemotherapy treatment to prevent re-accumulation of amyloid in the transplanted heart (**grade C recommendation; level IV evidence**).

Orthostatic Hypotension

- Orthostatic hypotension may respond to use of support stockings coupled with modest doses of fludrocortisone (**grade C recommendation; level IV evidence**).
- Midodrine is the most effective drug for orthostatic hypotension in patients with amyloidosis, but can cause supine hypertension (**grade C recommendation; level IV evidence**)

Bleeding

- There are no evidence-based recommendations for the management of bleeding in patients with amyloidosis (**grade C recommendation; level IV evidence**).
- Conventional supportive therapy should be considered. This may include factor replacement where coagulation assays indicate a need and platelet transfusion when the platelet count suggests that thrombocytopenia might be making a contribution to the bleeding. In addition, anti-fibrinolytic agents and local measures to secure haemostasis may be employed (**grade C recommendation; level IV evidence**.
- A conservative approach to surgery is recommended, and biopsies should not routinely be used to document the extent of organ involvement after the

initial diagnosis has been made. Liver biopsies are best avoided, or made via the trans-jugular route (**grade C recommendation; level IV evidence**.
- There are anecdotal reports of resolution of clotting abnormalities following treatment with chemotherapy and splenectomy but these are not substantive enough to form the basis of a clear recommendation (**grade C recommendation; level IV evidence**.

Experimental Approaches to Treatment

Future Directions

- Where possible patients receiving new therapies should be treated in the context of clinical trials (**grade C recommendation; level IV evidence**).

Multiple Myeloma and AL Amyloidosis

- Where myeloma and AL amyloidosis co-exist, choice of treatment for myeloma should take into account the extent of organ involvement with amyloid and the potential toxicities of individual treatments (**grade C recommendation; level IV evidence**).

Patient Information and Support

- The diagnosis needs to be communicated honestly to the patient with the minimum of delay. The information should be communicated in a quiet area with privacy, ideally in the company of a close relative and with the presence of a specialist nurse.
- Patients and their partners/carers should be given time to ask appropriate questions once they have been given the diagnosis; this may be best be done after an interval of a few hours or days.
- At the end of a consultation, it is recommended that patients and their family/carers are given written material which provides information on the condition. It should also guide patients and their family/carers on access to information services. IMF (UK) and the Leukaemia Research Fund produce useful, patient-orientated booklets on the condition and its treatment. Written information is also available from the National Amyloidosis Clinic (NAC).
- Patients need to be informed of the names of the key members of the specialist team or teams who are in charge of their care, and importantly, who is responsible for coordinating their care. Clear information on access to advice/support from the team should also be made available.
- The management plan needs to be communicated simply to the patient and his/her carer and should be clearly written in the case record so that the information is readily accessible to other members of the multi-disciplinary specialist team.
- Patients and their families should be cautioned about the amount of unregulated information accessible on the internet; they should be given recommendations to access appropriate sites, such as http://www.amyloidosis.org. An appropriately trained person, normally a specialist nurse, should be available to discuss/inform patients on information materials including guidance for using the internet as an information source.
- Patients should be given the opportunity of receiving more than one medical opinion.

Definitions:

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomised controlled trials

Ib Evidence obtained from at least one randomised controlled trial

IIa Evidence obtained from at least one well-designed, non-randomised study, including phase II trials and case-control studies

IIb Evidence obtained from at least one other type of well-designed, quasi-experimental study, i.e. studies without planned intervention, including observational studies

III Evidence obtained from well-designed, non-experimental descriptive studies. Evidence obtained from meta-analysis or randomised controlled trials or phase II studies which is published only in abstract form

IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

Grades of Recommendations

Grade A, evidence level Ia, Ib

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Grade B, evidence level IIa, IIb, III

Recommendation based on well-conducted studies but no randomised controlled trials on the topic of recommendation

Grade C, evidence level IV

Evidence from expert committee reports and/or clinical experiences of respected authorities

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most of the recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate diagnosis and appropriate management of AL amyloidosis, including control of disease, stabilization or regression of existing amyloid deposits, prevention of complications, preservation or improvement in the function of organs infiltrated by amyloid, improved quality of life, and prolonged survival

POTENTIAL HARMS

- The adverse effects of melphalan include myelotoxicity, and in patients who survive longer than 3.5 years, there is a 20% risk of myelodysplasia often leading to secondary leukaemia.
- Potential problems with the use of vincristine, adriamycin, dexamethasone (VAD) in AL amyloidosis are the cardiotoxicity of adriamycin, and, probably more importantly in practice, exacerbation of peripheral and autonomic neuropathy by vincristine.
- High-dose dexamethasone can cause severe fluid retention causing problems in patients with renal or cardiac amyloidosis, and can lead to bone fractures and vertebral collapse in those with bone involvement. Adriamycin has not been reported to exacerbate amyloid cardiomyopathy, but caution is recommended.
- There is a clear increase in the risk of venous thrombo-embolism in patients receiving thalidomide in combination with chemotherapy, but the risk is significantly lower in patients receiving thalidomide alone or with dexamethasone. Arterial thromboses may also occur.
- Patients with poor renal function and those who are already dialysis dependent fare very badly. In addition, patients with dominant or symptomatic cardiac amyloid have a very high treatment-related mortality (TRM).
- There is a significant risk, including death, associated with stem cell mobilization in patients with AL amyloidosis, even when granulocyte colony stimulating factor is used alone. Complications have included sudden onset of pulmonary oedema, and/or an unexplained syndrome of progressive hypoxia and hypotension, which may occur in patients without cardiac amyloid
- The chief adverse effect of midodrine is supine hypertension, and other pressor agents must be co-administered with caution.

CONTRAINDICATIONS

CONTRAINDICATIONS

- Calcium-channel blockers and beta-blockers are contraindicated in cardiac amyloidosis.
- Cardiac amyloidosis is a relative contraindication to the use of digoxin.

QUALIFYING STATEMENTS

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While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Guidelines Working Group of UK Myeloma Forum, British Committee for Standards in Haematology, British Society for Haematology. Guidelines on the diagnosis and management of AL amyloidosis. Br J Haematol 2004 Jun;125(6):681-700. [62 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2004 Jun

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

The UK Myeloma Forum AL amyloidosis Guidelines Working Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Working Group Members: Jenny Bird, Avon Haematology Unit, Bristol Haematology and Oncology Centre, Bristol; Jamie Cavenagh, St Bartholomew's and The Royal London School of Medicine and Dentistry, Royal Free Hospital, London; Philip Hawkins, National Amyloidosis Centre, Royal Free Hospital, London; Helen Lachmann, National Amyloidosis Centre, Royal Free Hospital, London; Atul Mehta, Royal Free Hospital, London; and Diana Samson, Imperial College, London (*Chairman, UK Myeloma Forum*).

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

The planned date for full revision of these guidelines by the Guidelines Working Group of the UK Myeloma Forum is January 2007. Interim updates will be on the UK Myeloma Forum and BCSH websites.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from Dr Jenny Bird, Avon Haematology Unit, Bristol Haematology and Oncology Centre, Horfield Road, Bristol BS2 3ED, UK. E-mail: jenny.bird@ubht.swest.nhs.uk

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 26, 2006. The information was verified by the guideline developer on October 25, 2006.

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